REMARKS

Prior to entry of this amendment, claims 1-4, 6, 8, 10-12, 16, 20-28, 32-25, 44, 45, 47, 48, 52 and 67-89 were pending. Claims 6, 21 and 22 are canceled herein and no new claims are added. Thus, after entry of this amendment, **claims 1-4, 8, 10-12, 16, 20, 23-28, 32-35, 44, 45, 47, 48, 52 and 67-89 will be pending**. Of these, claims 32-35, 44, 45, 47, 48, 76-79 and 86-89 are currently withdrawn.

Claims 23, 67, 68, 70, 80 and 82 are amended to recite the biological deposit information for the HuCC49V10 antibody. Claims 80 and 82 are further amended to correct a typographical error. No new matter is introduced by these amendments and no amendments are made to distinguish prior art.

The Office states on page 2 of the Office action that a Request for Continued Examination (RCE) was filed for this application. However, Applicants point out that the Amendment and Response filed May 28, 2008 was submitted in response to a non-final Office action and did not accompany a RCE.

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1-4, 6, 8, 10-12, 16, 23-28, 52, 68 and 80 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement for the reasons of record. In particular, the Office maintains that the specification does not reasonably enable humanized CC49 antibodies and antigen-binding fragments thereof "comprising a non-conservative amino acid substitution at any position OR at any tyrosine residue of L-CDR3 OR substituting the tyrosine residue at position 91 with any amino acid." The Office further maintains that the claims are not enabled for a humanized CC49 antibody comprising "a non-conservative substitution at any residue in the L-CDR3 and a substitution at any residue in any L-CDR or H-CDR of the antibody." The Office concludes it would require undue experimentation to practice the claimed invention. Applicants traverse this rejection.

An analysis to determine if a claim is fully enabled by the specification requires an evaluation of whether the specification contains sufficient guidance and information to allow one of skill in the art to *make and use* the claimed invention, *without undue experimentation*. The standard for determining whether a claim is enabled is not whether experimentation is required, but whether it is unreasonable or undue. As stated in MPEP 2164.01, "The fact that experimentation may be complex does not

necessarily make it undue, if the art typically engages in such experimentation" (*In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174). Applicants submit that although some experimentation is required to practice the full scope of the claimed invention, the experimentation is not undue or unreasonable, and it is routinely practiced by those of skill in the art.

In order to determine whether the experimentation required to make and use the claimed invention is undue, a variety of factors must be considered, including those discussed below (*In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Breadth of the claims

Claim 1 and dependent claims 2-4, 8, 10-12, 16 and 52 are directed to a humanized CC49 antibody comprising a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3, all of a parent CC49 antibody, wherein the L-CDR3 or an antigen binding fragment of the humanized CC49 antibody comprises a non-conservative amino acid substitution, and has a high binding affinity for TAG-72 compared to the parent CC49 antibody (HuCC49V10). Claim 68 further requires that the non-conservative amino acid substitution is at position 91. The scope of each of these claims is limited to humanized CC49 antibodies having all six CDRs from the parent CC49 antibody and comprising a non-conservative amino acid substitution in either L-CDR3 or an antigen binding fragment of the humanized CC49 antibody.

Claim 23 and dependent claims 24-28 are directed to a humanized CC49 antibody comprising four variable light framework regions and four variable heavy framework regions; a L-CDR1, a L-CDR2, a L-CDR3, a H-CDR1, a H-CDR2 and a H-CDR3, wherein at least one CDR is a human antibody CDR and the remaining CDRs are a murine CC49 antibody CDR; a non-conservative substitution of a first residue, wherein the first residue is in the L-CDR3 of the antibody; and a substitution of a second residue, wherein the second residue is in any L-CDR or H-CDR of the antibody, wherein the humanized CC49 antibody has a high binding affinity for TAG-72 and is minimally immunogenic compared to the parent HuCC49V10 antibody. Claim 80 further specifies that the all six CDRs are from HuCC49V10 and the first non-conservative substitution is at position 91 in the L-CDR3 and the second substitution is at position 27b of L-CDR1. Each of these claims is limited to humanized CC49 antibodies comprising CDRs from either mouse CC49 or a human antibody, wherein the antibodies comprise two substitutions, the first in L-CDR and the second in any CDR.

Nature of the invention

The nature of the claimed invention is directed to humanized antibodies derived from a murine CC49 antibody. The antibodies bind tumor-associated glycoprotein (TAG)-72 with high affinity and are minimally immunogenic. The humanized antibodies are altered to contain a non-conservative amino acid substitution in L-CDR3, and optionally a second substitution in another CDR, in order to improve binding affinity.

Level of skill of one of ordinary skill in the art

The level of skill in the art is high. Skilled practitioners in this art generally have advanced degrees with several years of experience in the generation and characterization of antibodies.

Level of predictability in the art

The Office argues that the level of unpredictability in the art is high. Applicants do not refute that some experimentation is required to determine which non-conservative variants result in antibodies that exhibit increased binding affinity and decreased immunogenicity relative to the parent antibody. However, the experimentation required was routinely practiced by the skilled artisan as of the priority date of the application and does not rise to the level of undue or unreasonable experimentation.

State of the prior art

As of the priority date of the application, the sequences of the CC49 and HuCC49V10 antibodies were well known (see Tamura *et al., J. Immunol.*, 164:1432-1441, 2000, a copy of which was provided with the Amendment and Response filed May 28, 2008; PCT Application Nos. PCT/US89/04402 and PCT/US99/25552). It was also well known how to synthesize proteins, such as recombinant humanized antibodies, make functional variants thereof and test recombinant antibodies for affinity and immunogenicity. The procedures required to introduce mutations into the CDRs of antibodies and evaluate the recombinant antibodies for an alteration in binding affinity and immunogenicity were routinely practiced in the art as of the priority date of this application.

Amount of direction provided & existence of working examples in the specification

The specification describes the CC49 and HuCC49V10 antibodies, and the sequences of these antibodies were available as of the priority date of the application. Furthermore, the specification explicitly teaches, and provides working examples, of the following:

(i) methods of generating a recombinant library of genes encoding antibody variants (page 34, line 23 through page 40, line 5);

(ii) methods of producing whole antibodies or Fab antibody fragments (page 40, lines 8 through page 42, line 8; page 45, line 10 through page 48, line 20);

(iii) methods of screening Fab antibody variants that bind to an antigen, for example, TAG-72 (page 40, lines 8 through page 45, line 8); and

(iv) methods of testing variant whole antibodies for antigen binding activity and immunoreactivity (page 47, line 1 through page 48, line 2; page 48, line 22 through page 53, line 23).

Moreover, the specification discloses the synthesis and testing of multiple antibody variants, in addition to the HuCC49V10-14 and HuCC49V10-15 antibodies. Based on the binding affinity and immunogenicity testing disclosed in the specification, Applicants determined whether a variant antibody had high binding affinity for TAG-72 and/or minimal immunogenicity, compared to a parent CC49 antibody. Although the application discloses only two variants (HuCC49V10-14 and HuCC49V10-15) that exhibit the desired properties of improved affinity and decreased immunogenicity, the disclosure of several other variants (for example, HuCC49V10-7, -10, -12 and -13) comprising substitutions in other CDR residues provides additional guidance to one of skill in the art for selecting appropriate residues for mutation.

Quantity of experimentation needed to make or use the invention based on the content of the disclosure

Although some experimentation is required to practice the claimed invention, the specification provides sufficient guidance to direct one of ordinary skill in the art to select appropriate CDR mutations. As described above, the specification teaches both functional *(i.e.* increased binding affinity, decreased immunogenicity) and non-functional variants of the humanized antibodies, thereby arming the ordinary artisan with information on which substitutions work and which do not. In addition, the claims limit the number of possible recombinant antibodies that can be made and remain within the scope of the claimed antibodies.

Summary

Applicants submit that when each of the above *Wands* factors are considered together, the experimentation required to make and use the claimed invention is not undue. In particular, given the high level of skill in the art, the information available in the prior art, and the specific guidance and working examples provided in the specification, one would merely need routine experimentation to (i) make humanized CC49 antibodies having the claimed genus of residue substitutions and (ii) test these antibodies for their binding affinity and immunogenicity. Accordingly, Applicants submit that the pending claims are fully enabled by the specification and respectfully request that this rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

CLAIM OBJECTIONS

Claims 80 and 82 are objected to for the recitation of "H-CDR3of." Although the Office action indicates claims 80 and 83 are objected to, Applicants believe the Office intended to object to claims 80 and 82, both of which recite "H-CDR3of." Claims 80 and 82 are amended herein to replace "H-CDR3of" with "H-CDR3 of." Accordingly, Applicants request withdrawal of this objection.

Claim 6 is objected to for failing to further limit the subject matter of claim 1, from which it depends. Claim 6 is canceled herein, rendering the rejection moot.

REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 23-28, 67-75 and 80-85 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Specifically, the Office states that the claims are vague and indefinite for reciting "HuCC49V10" in claims 23, 67, 68, 70, 80 and 82 as the only means of identifying the antibody. In response, claims 23, 67, 68, 70, 80 and 82 are amended to recite the biological deposit information for HuCC49V10 (ATCC Accession No. PTA-5416). Accordingly, Applicants request withdrawal of this rejection under 35 U.S.C. §112, second paragraph.

ALLOWED CLAIM

Applicants thank the examiner for indicating that claim 20 is allowed.

REQUEST FOR REJOINDER

The Examiner has required a restriction between product and process claims. Applicants have elected claims to a specific product. Applicants expressly request that the method claims (claims 32-35, 44, 45, 47, 48, 76-79 and 86-89) be rejoined and the claims examined, at the latest upon the allowance of any of the product claims.

CONCLUDING STATEMENT

Applicants believe that the foregoing comprises a full and complete response to the Office action of record. Withdrawal of the pending rejections and reconsideration of the claims is respectfully requested. If the Examiner believes that there are any remaining issues in the case that could be resolved by a telephonic interview, the Examiner is encouraged to contact the representative for Applicants listed below to discuss any outstanding matters.

Respectfully submitted,

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